REMARKS

Upon entry of this amendment, claims 1, 14-25, 27, 38, 43, and 46-48 will be pending in the application. Claims 1, 38, 43, and 48 are amended to recite PMS2-134 and PMSR3 and genetic stability. Claim 25 is amended to provide proper syntax. No new matter is introduced by this amendment.

As an initial matter, Applicants respectfully acknowledge that the present claims are rejected for alleged obviousness-type double patenting over claims of U.S. Application Serial No. 09/780,675. Applicants respectfully request that the rejections be held in abeyance until an indication of allowable claims is received.

Claims 1, 14-25, 38, 43, 47, and 48 are described.

Claims 1, 14-25, 38, 43, 47, and 48 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of written description. Applicants disagree with the rejection. Nonetheless, in an effort to advance prosecution of the application, Applicants have amended claims 1, 38, 43, and 48. Withdrawal of the rejection is respectfully requested.

Claims 1, 14-15, 38, 43, 47, and 48 are enabled.

Claims 1, 14-25, 38, 43, 47, and 48 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicants disagree with the rejection. Nonetheless, in an effort to advance prosecution of the application, Applicants have amended claims 1, 38, 43, and 48 to overcome the rejection. Withdrawal of the rejection is respectfully requested.

Claims 1, 15, 27, 38, and 42 are patentable over Nicolaides 1, Iris, and Morris.

Claims 1, 15, 27, 38, and 42 are rejected under 35 U.S.C. § 103 for alleged obviousness over Nicolaides 1 (United States Published Application 2002/0068284), U.S. Patent No. 6,221,585 to Iris *et al.* ("Iris"), and Morris *et al.* (*J. Infect. Dis.*, 171:954-960 (1995)) ("Morris"). Applicants respectfully request reconsideration and withdrawal of the rejection because one skilled in the art would not have considered the Morris or Iris reference in seeking to develop a method for creating multi-antibiotic resistant bacteria according to the methods of Nicolaides 1.

Nicolaides 1 describes a cell expressing a dominant negative mismatch repair (MMR) gene as having an altered mismatch control pathway, which thereby alters a gene or set of genes controlling a *single* phenotype. (Nicolaides 1, [0058].) In other words, Nicolaides 1 describes a hypermutable bacterium having one or more mutations resulting in any *one* of a number of altered phenotypes, such as resistance to an antibiotic (*e.g.*, kanamycin) (Nicolaides 1, [0058]), heat resistance, or high recombinant protein production (Nicolaides 1, Example 3). There is no teaching or suggestion in the description of Nicolaides 1 of a single cell exhibiting resistance to multiple antibiotics.

The Iris reference describes a method for identifying genes associated with a phenotype of interest. According to that method, a phenotype of interest is identified and then a population of nucleic acid molecules from a population having the phenotype of interest is compared to a second population of nucleic acid molecules not having the phenotype of interest. (Iris, col. 8., lines 18-32.) The method described by Iris, however, requires homogenization of the populations of nucleic acids being compared. (*Id.*) One skilled in the art would not have been motivated by the Iris reference to create hypermutable bacteria having randomized mutations throughout their genome according to the methods of Nicolaides 1 in an effort to arrive at the present invention.

In order for genes associated with a phenotype of interest to be identified according to the method described by the Iris reference, one skilled in the art would not have induced hypermutability in such a cell as described by Nicolaides 1.

The Morris reference describes multidrug resistance of *M. tuberculosis* mediated by an accumulation of mutations in genes encoding drug targets. The Morris reference, however, does not teach, suggest, or motivate one skilled in the art to generate bacteria having multiantibiotic resistance. Rather, the aim of the Morris reference is to prevent such resistance. One skilled in the art thus would not have considered the Morris reference in seeking to develop a method for *creating* multi-antibiotic resistant bacteria. In other words, one skilled in the art would not have been motivated by the Morris reference to generate multiantibiotic-resistant bacteria according to the methods of Nicolaides 1 in seeking to arrive at the present invention.

As one skilled in the art would not have been motivated by the Iris or Morris references to generate bacteria having multiantibiotic resistance according to the methods of Nicolaides 1, withdrawal of the rejection is respectfully requested.

Claims 1, 19, 27, and 38 are patentable over Iris in view of Stemmer, Johnston, Aronshtam, LeClerc, Drummond, Moreland, and Morris.

Claims 1, 19, and 38 are rejected under 35 U.S.C. § 103 for alleged obviousness over U.S. Patent No. 6,221,585 to Iris *et al.* ("Iris") in view of U.S. Published Application 2002/0049104 to Stemmer *et al.* ("Stemmer"), U.S. Patent No. 6,043,048 to Johnston *et al.* ("Johnston"), Aronshtam and Marinus (*Nuc. Acids Res.*, 24(13):2498-2504 (1996)) ("Aronshtam"), LeClerc *et al.* (*Science*, 274:1208-1211 (1996)) ("LeClerc"), Drummond *et al.* (*J. Biol. Chem.*, 271(33):19645-19648 (1996)) ("Drummond"), Moreland *et al.* (*Cancer Res.*, 59:2102-2104 (1999)) ("Moreland"), and Morris *et al.* (*J. Infect. Dis.*, 171:954-960 (1995)) ("Morris"). Applicants disagree with the rejection. Nonetheless, Applicants respectfully assert that the amendments to the claims made herein overcome the rejection. Withdrawal of the rejection is thus respectfully requested.

Claims 1, 27, and 38 are patentable over Iris in view of Stemmer, Johnston, and either of Nicolaides 2 or Nicolaides 3, further in view of LeClerc, Drummond, Moreland, and Morris.

Claims 1, 27, and 38 are rejected for alleged obviousness over Iris in view of Stemmer, Johnston, and either of Nicolaides 2 (Nicolaides *et al.*, *Mol. Cell. Biol.*, 18(3):1635-1641 (1998)) or Nicolaides 3 (U.S. Patent No., 6,146,894), further in view of LeClerc, Drummond, Moreland, and Morris. Applicants traverse the rejection because one skilled in the art would not have been motivated to combine the cited references.

As explained above, the Iris reference describes a method for identifying genes associated with a phenotype of interest. According to that method, a phenotype of interest is identified and then a population of nucleic acid molecules from a population having the phenotype of interest is compared to a second population of nucleic acid molecules not having the phenotype of interest. (Iris, col. 8., lines 18-32.) The method described by Iris, however, requires homogenization of the populations of nucleic acids being compared. (*Id.*) One skilled in the art would not have been motivated by the Iris reference to create

hypermutable bacteria having randomized mutations throughout their genome according to the methods of Nicolaides 2 or 3 in an effort to arrive at the present invention.

The LeClerc, Drummond, Moreland, and Morris references are alleged by the Office Action to show that "those in the art would have had a reasonable expectation that introducing defective mismatch repair would be effective at generating bacterial cells with antibiotic resistant phenotypes." (Office Action at page 9.) Stemmer is cited for its alleged suggestion of the introduction of a mismatch repair deficiency. (*Id.*)

The Drummond reference describes the introduction of a dominant negative p53 gene into cancer cells to increase resistance to cisplatin. Similarly, the Moreland reference describes the use of aphidicolin to increase sensitivity of cancer cells to methylating agents. One skilled in the art would not have considered the Drummond or Moreland reference in combination with either Nicolaides 2 or 3 an effort to create hypermutable *bacterial cells* according to the present invention.

The aim of the LeClerc reference is to identify pre-existing mutator strains with a goal of identifying a mechanism to *prevent* such mutation. For example, the LeClerc reference suggests an antisense strategy for preventing a mutator phenotype. (LeClerc at page 1210.) Likewise, the Morris reference describes multidrug resistance of *M. tuberculosis* mediated by an accumulation of mutations in genes encoding drug targets. The Morris reference, however, does not teach, suggest, or motivate one of ordinary skill in the art to *generate* bacteria having multiantibiotic resistance. Rather, the aim of the Morris reference is to prevent the generation of bacteria having such resistance. One skilled in the art thus would not have considered the LeClerc or Morris reference in combination with Nicolaides 2 or 3 in seeking to develop a method for *creating* hypermutable bacteria having multiantibiotic resistance according to the present invention.

In addition, the Stemmer and Iris references propose two wholly different methods for identifying genes associated with a phenotype. The methods of the Stemmer reference rely on generation of genetic diversity of chimeric nucleotide sequences. In the Stemmer method, members of a library of diverse conjoint polynucleotides are introduced into a host cell for expression and selection. (Stemmer, [0054].) Vectors conferring a desired phenotype are recovered and subjected to diversification until an optimized set of elements are identified. (Stemmer, Figures 3 and 4.) Thus, the method of Stemmer begins with a nucleic acid

molecule having an unknown function and derives the phenotype associated therewith. In contrast, the Iris reference first identifies a phenotype of interest and then compares a *homogeneous* population of nucleic acid molecules from a population having the phenotype of interest to a second *homogeneous* population of nucleic acid molecules not having the phenotype of interest. (Iris, Col. 8.) In short, the methods of Iris and Stemmer are completely contrasting approaches to identifying genes associated with a phenotype which the ordinarily skilled artisan would not have been motivated to combine.

The present Office Action acknowledges the differences between the modes of operation of the methods of the Stemmer and Iris references but asserts that "while the methodologies of the two references vary, certain teachings of the references have common applicability to the problem at hand.... [A]lthough those in the art may not have been motivated to combine the particulars of the methods, certain teachings of the references ... would have common applicability that those in the art would be motivated to introduce into alternative methodologies of dealing with the same problem." (Office Action at page 11.) Such piecemeal construction of the present invention by combination of select elements of the cited references amounts to impermissible hindsight reasoning. "It is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965).

In short, Applicants assert that a *prima facie* case of obviousness of claims 1, 27, and 38 has not been established on this record. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 14-25, 27, and 38 are patentable over either of (A) Iris, Stemmer, Johnston, and Aronshtam or (B) Iris, Stemmer, Johnston, either of Nicolaides 2 or 3, LeClerc, Drummond, Moreland, Morris, Lin, Chang, Setterstrom, and The Merck Index.

Claims 1, 14-25, 27, and 38 are rejected for alleged obviousness over either of (A) Iris, Stemmer, Johnston, and Aronshtam or (B) Iris, Stemmer, Johnston, either of Nicolaides 2 or 3, LeClerc, Drummond, Moreland, Morris, U.S. Patent No. 6,025,400 to Lin ("Lin"),

U.S. Patent No. 6,043,220 to Chang *et al.* ("Chang"), U.S. Patent No. 6,410,056 to Setterstrom *et al.* ("Setterstrom"), and The Merck Index (1983, pages 2036, 5032-5033, and 6448-6449). Applicants respectfully disagree with the rejection.

Applicants respectfully assert that the amendments to the claims overcome the rejection for alleged lack of obviousness of claims 1, 19, 27, and 38 in view of the Iris, Stemmer, Aronshtam, Johnston, LeClerc, Drummond, Moreland, and Morris references.

Applicants further respectfully assert that the above remarks regarding the lack of obviousness of claims 1, 27, and 38 in view of the Iris, Stemmer, Johnston, Nicolaides 2 or Nicolaides 3, LeClerc, Drummond, Moreland, and Morris references are equally applicable to the present rejection.

Furthermore, bacterial resistance to a plurality of antibiotics including those listed in claims 14-25 has not been established. The Lin, Chang, and Setterstrom references and The Merck Index are relied upon for the alleged showing that the antibiotics of claims 14-25 were known in the art. However, no motivation to combine those references with any of Iris, Stemmer, Aronshtam, Johnston, Nicolaides 2 or Nicolaides 3, LeClerc, Drummond, Moreland, and Morris or a reasonable expectation of success in generating resistance to the antibiotics identified by introducing a dominant negative allele of a mismatch repair gene into bacteria has been established on the present record. Absent these elements, a *prima facie* case of obviousness of claims 1, 14-25, 27, and 38 cannot be demonstrated. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 14-25, 27, 38, 43, and 46-48 are patentable over Nicolaides 1 in view of the Iris and Morris references and further in view of the Stemmer, Lin, Chang, and Setterstrom references and The Merck Index.

Claims 1, 14-25, 27, 38, 43, and 46-48 are rejected for alleged obviousness over Nicolaides 1 in view of the Iris and Morris references and further in view of the Stemmer, Lin, Chang, and Setterstrom references and The Merck Index. Applicants disagree with the rejection.

Nicolaides 1 describes a cell expressing a dominant negative mismatch repair (MMR) gene as having an altered mismatch control pathway, which thereby alters a gene or set of genes controlling a *single* phenotype. (Nicolaides 1, [0058].) In other words, Nicolaides 1

describes a hypermutable bacterium having one or more mutations resulting in any *one* of a number of altered phenotypes, such as resistance to an antibiotic (*e.g.*, kanamycin) (Nicolaides 1, [0058]), heat resistance, or high recombinant protein production (Nicolaides 1, Example 3). There is no teaching or suggestion in the description of Nicolaides 1 of a single cell exhibiting resistance to multiple antibiotics.

The Iris reference describes a method for identifying genes associated with a phenotype of interest. According to that method, a phenotype of interest is identified and then a population of nucleic acid molecules from a population having the phenotype of interest is compared to a second population of nucleic acid molecules not having the phenotype of interest. (Iris, col. 8., lines 18-32.) The method described by Iris, however, requires homogenization of the populations of nucleic acids being compared. (*Id.*) One skilled in the art would not have been motivated by the Iris reference to create hypermutable bacteria having randomized mutations throughout their genome according to the methods of Nicolaides 1 in an effort to arrive at the present invention.

In order for genes associated with a phenotype of interest to be identified according to the method described by the Iris reference, one skilled in the art would not have induced hypermutability in such a cell as described by Nicolaides 1.

The Morris reference describes multidrug resistance of *M. tuberculosis* mediated by an accumulation of mutations in genes encoding drug targets. The Morris reference, however, does not teach, suggest, or motivate one skilled in the art to generate bacteria having multiantibiotic resistance. Rather, the aim of the Morris reference is to prevent such resistance. One skilled in the art thus would not have considered the Morris reference in seeking to develop a method for *creating* multi-antibiotic resistant bacteria. In other words, one skilled in the art would not have been motivated by the Morris reference to generate multiantibiotic-resistant bacteria according to the methods of Nicolaides 1 in seeking to arrive at the present invention.

Additionally, as previously described, the methods of Iris and Stemmer are completely contrasting approaches to identifying genes associated with a phenotype which the skilled artisan would not have been motivated to combine.

Furthermore, bacterial resistance to a plurality of antibiotics including those listed in claims 14-25 has not been established. The Lin, Chang, and Setterstrom references and The

Merck Index are relied upon for the alleged showing that the antibiotics of claims 14-25 were known in the art. However, no motivation to combine those references with any of Iris, Stemmer, Nicolaides 1, and Morris or a reasonable expectation of success in generating resistance to the antibiotics identified by introducing a dominant negative allele of a mismatch repair gene into bacteria has been established on the present record. Absent these elements, a *prima facie* case of obviousness of claims 1, 14-25, 27, 38, 43, and 46-48 cannot be demonstrated.

As one skilled in the art would not have been motivated by the Iris, Stemmer, or Morris references to generate bacteria having multiantibiotic resistance to the compounds described by the Lin, Chang, and Setterstrom references and The Merck Index according to the methods of Nicolaides 1, withdrawal of the rejection is respectfully requested.

Claims 27 and 46 are patentable over either of (A) Iris, Stemmer, Johnston, and Aronshtam or (B) Iris, Stemmer, Johnston, either of Nicolaides 2 or 3, LeClerc, Drummond, Moreland, Morris, Lin, Chang, Setterstrom, and The Merck Index and further in view of Nicolaides 1.

Claims 27 and 46 are rejected for alleged obviousness over either of (A) Iris, Stemmer, Johnston, and Aronshtam or (B) Iris, Stemmer, Johnston, either of Nicolaides 2 or 3, LeClerc, Drummond, Moreland, Morris, Lin, Chang, Setterstrom, and The Merck Index and further in view of Nicolaides 1. Applicants disagree with the rejection.

For the reasons previously described, one skilled in the art would not have combined Nicolaides 1, 2, or 3 with Iris; one skilled in the art would not have considered the Drummond or Moreland reference in combination with either Nicolaides 1, 2, or 3 an effort to create hypermutable bacterial cells according to the present invention; one skilled in the art would not have considered the LeClerc or Morris reference in combination with Nicolaides 1, 2, or 3 in seeking to develop a method for creating hypermutable bacteria having multiantibiotic resistance according to the present invention. Additionally, no motivation to combine the Lin, Chang, Setterstrom, and The Merck Index references with any of Iris, Stemmer, Nicolaides 2 or 3, Nicolaides 1, and Morris or a reasonable expectation of success in generating resistance to the antibiotics identified by introducing a dominant negative allele of a mismatch repair gene into bacteria has been established on the present record.

As one skilled in the art would not have been motivated to combine the cited references to arrive at the present invention, withdrawal of the rejection is respectfully requested.

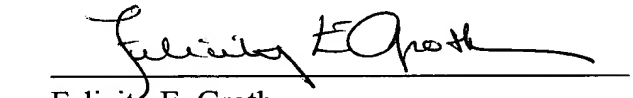
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-557-5908.

Respectfully submitted,

Date: June 27, 2005



Felicity E. Groth
Registration No. 47,042

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439